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REVIEW ARTICLE

Position statement: topical calcineurin inhibitors in atopic dermatitis

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Abstract

Background Atopic dermatitis (AD) is a common inflammatory skin disease in both adults and children. Whilst topical calcineurin inhibitors (TCIs), tacrolimus ointment and pimecrolimus cream, have proven efficacy for the treatment of AD, it is important to involve experts to obtain their opinion on its optimal treatment.

Objective Using a modified Delphi approach, this project aimed to generate consensus amongst experts on the use of TCIs in the treatment of AD, with a focus on the differentiation between tacrolimus and pimecrolimus.

Methods Six expert dermatologists from different European countries participated in this project based on their experience with AD and its treatment, which was evaluated by literature analysis and expert opinion. Consensus amongst the experts was generated using a modified Delphi approach, consisting of three distinct phases, during which a web meeting (June 2017), two online rounds of blinded Delphi voting (July–September 2017) and a face-to-face meeting (November 2017) were conducted. The consensus statements concerned two main topics: (i) Background of AD; and (ii) TCIs in AD. Hot topics in the treatment of AD not supported by meta-analysis, clinical trials or large observational studies were also discussed based on clinical experience.

Results In total, 25 consensus statements were defined and validated: eight statements on the general background of AD and 17 statements on the use of TCIs in AD, including their mechanism of action and therapeutic indications in AD, efficacy in adult and paediatric AD patients, pharmacokinetics, incidence of adverse events and safety concerns. Hot topics on the use of TCIs for the treatment of AD included cream vs. ointment, dosages, TCIs contact allergy, burning sensation management, superinfection and vaccination concerns.

Conclusion Topical calcineurin inhibitors are a suitable therapy for AD, and selection of the specific TCI should be based on factors which differentiate tacrolimus from pimecrolimus.

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Conflicts of interest

Whilst LEO Pharma is the manufacturer of tacrolimus ointment and the supporter of the project, there was no industry bias and the manuscript contents reflect entirely the Authors' opinions without any influence by the sponsor. AR declares she has been involved in clinical studies, consultations and lectures by Astellas Pharma, LEO Pharma, Novartis, Regeneron, Sanofi and Roche. AM declares he has been involved in lectures and consultations by Astellas Pharma and LEO Pharma. ESB declares she has been involved in clinical studies, consultations and lectures by Novartis, Sanofi, Pierre FAbre, GSK and LEO Pharma. EV received lecture honoraria from Novartis, LEO Pharma, Meda Pharmaceuticals, Pierre Fabre, La Roche Posay and Hippocrates Sintech, and participated in clinical trials from Genesis, AbbVie, Pfizer, Janssen and Sanofi. AK and ODP declare no conflict of interests.

Funding source

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Introduction

Atopic dermatitis (AD) represents the most common inflammatory skin disease in both adults and children.[1,2] It is a chronic skin condition, with a major impact on the quality of life of affected patients and their families.[2,3]

Figure 1 depicts a detailed treatment pathway for mild, moderate and severe AD. Topical corticosteroids are considered the first-line therapy for AD.[4,5] However, their long-term use can be associated with relevant side-effects, and patients may be reluctant to continue this therapy given the risk of adverse events, ultimately contributing to treatment failure.[6–8]

Two topical calcineurin inhibitors (TCIs), tacrolimus ointment and pimecrolimus cream, have proven efficacy for the treatment of AD.[7] Whilst they are both inhibitors of calcineurin, tacrolimus and pimecrolimus have distinct pharmacological and efficacy profiles.[7] Consequently, the selection of therapy should rely mostly on field-practice experience and robust expert opinion of existing evidence and factors able to differentiate between the two drugs.[6,7]

Due to the burden of AD, it is important to involve experts to obtain their opinion on its optimal treatment. This paper represents the final outcome of a European project aimed at obtaining, using a modified Delphi approach, expert opinion to reach consensus on TCIs in the treatment of AD, with a focus on the differentiation between tacrolimus and pimecrolimus.

Methods

Six expert dermatologists from different European countries participated in this project based on their experience with AD and its treatment, which was evaluated by literature analysis and expert opinion. Consensus amongst the experts was generated by a modified Delphi approach, consisting of three distinct phases: an Exploration phase, an Analytical phase and an Evaluation phase.

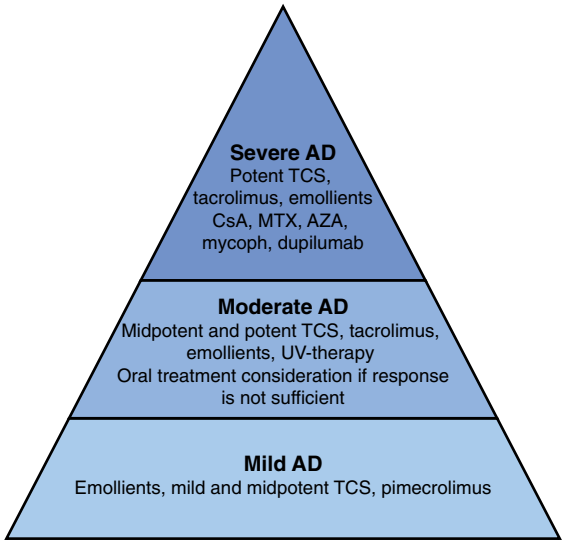

Figure 1 Treatment pathway for mild, moderate and severe atopic dermatitis (AD). AZA, azathioprine; CsA, cyclosporine A; MTX, methotrexate; TCS, topical corticosteroids; UV, ultraviolet.

Exploration phase

During the Exploration phase, the expert panel identified objectives and arguments to be evaluated, detailed the methodology, and prepared comprehensive documentation of research questions and preliminary statements based on the literature. An online meeting was conducted (June 2017) during which general background consensus statements were defined based on expert opinion and literature data. Literature research was conducted using the following databases: PubMed/MEDLINE/PreMEDLINE. Relevant articles were identified based on specific selected criteria/keywords with reproducible methods (see Appendix).

The consensus statements concerned two main topics: (i) Background of AD; and (ii) TCIs in AD, which was separated into five research questions: (i) What about the mechanism of action and therapeutic indications in AD? (ii) What about efficacy in adult and paediatric AD patients? (iii) What about pharmacokinetics? (iv) What about the incidence of adverse events? and (v) What about the safety concerns?

Hot topics in the treatment of AD not supported by meta-analysis, clinical trials or large observational studies (i.e. without major literature evidence) were also identified.

Analytical phase

This phase involved statement processing based on expert opinion and literature data. The first round of online Delphi voting was conducted. In total, two rounds of online Delphi voting were conducted (July–September 2017), with participants blinded to the results of other experts. A secure website (survey monkey.com) was used for the online voting, with Verisign certificate version 3, 128-bit encryption.

The degree of consensus for each statement was assessed using a 5-point unipolar Likert scale: agreement was set at a cut-off of 80% of positive responses (corresponding to scores 4 and 5 on the Likert scale).

Evaluation phase

Delphi results from round 1 voting were submitted to the expert panel for evaluation, and statements were modified according to participants' feedback and were then voted on again in their modified form during the second round of online Delphi voting. Lastly, a face-to-face meeting was conducted in November 2017 during which the final consensus statements were selected, based on the pre-identified cut-off value of 80%, expert opinions on hot topics in the treatment of AD without major literature evidence were collected, and

Table 1 Consensus statements on the general background of atopic dermatitis (AD)

Statement		Consensus reached (%)
1A	AD is an inflammatory, itching, chronic or chronically relapsing skin disease	100
1B	AD is one of the most common skin diseases which affects adults and mainly children in most countries of the world and which occurs often in families with history of other atopic diseases (bronchial asthma and/or allergic rhinoconjunctivitis)	100
1C	After establishing the diagnosis of AD, the severity of the disease has to be determined. The standard approach is the 'Scoring of Atopic Dermatitis' (SCORAD). Another commonly used scale to assess disease severity is the Eczema Area and Severity Index (EASI). **SCORAD (<25 mild AD, ≥25 and ≤50 moderate AD, >50 severe AD). EASI (≤7 mild AD, >7 and ≤21 moderate AD, >21 severe AD)	100
1D	Management of exacerbated AD is a therapeutic challenge, as it requires effective short-term control of acute symptoms, without compromising the overall management plan that is aimed at long-term stabilization, flare prevention and avoidance of side-effects	100
1E	Anti-inflammatory treatment based on topical glucocorticosteroids (GCs) and topical calcineurin inhibitors (TCIs) is used for the management of exacerbations and, more recently, for proactive therapy in selected cases	83.33
1F	Topical GCs remain the mainstay of therapy with fast and effective action. However, they are associated with some adverse effects, especially over the long-term period. In contrast, tacrolimus has a more specific mechanism of action and TCIs, due to their high affinity for the receptor and lower absorption through skin, do not cause such events. TCIs are especially indicated in long-term therapies and are preferred in certain sensitive areas (TCIs are especially indicated in challenging areas such as the face, intertriginous sites and anogenital area)	100
1G	TCIs should be used as a second-line drug following topical GCs	83.33
1H	The anti-inflammatory potency of tacrolimus ointment is similar to that of a corticosteroid with moderate activity, whilst the latter is more active than pimecrolimus cream	100

'field-practice' clinical experience and real-life clinical data were discussed.

It should be highlighted that a Delphi consensus is not a method for introducing new or better evidence, and it only proposes a process to identify rational choices on important topics. Strengths and limitations of the modified Delphi approach include the following. Firstly, although there were a relatively small number of selected expert panelists, the participation of opinion leaders from multiple countries granted broader sharing and increased the consistency of the structured report. Secondly, the discussion between scientific board members may have influenced the expert opinion leading to higher percentages of final agreement. Thirdly, more recent data may have been published subsequent to the literature search, which was performed in June 2017.

The entire project was handled by a professional agency (Hippocrates, Genoa, Italy), which provided support for the literature research and in conducting meetings and Delphi rounds.

Consensus statements and Delphi results

After two rounds of voting, all statements reached final consensus. In total, 25 consensus statements were defined and validated: eight statements on the general background of AD and 17 statements on the use of TCIs in AD, including their mechanism of action, efficacy, pharmacokinetics, incidence of adverse events and safety concerns. The final version of the statements for each topic and research question, and the level of consensus achieved are depicted in Tables 1–6.

A detailed comment on the statements is provided below.

Table 2 Consensus statements on the mechanism of action and therapeutic indications of topical calcineurin inhibitors (TCIs) in atopic dermatitis (AD)

Statement		Consensus reached (%)
2A	There are two TCIs available for AD treatment: tacrolimus 0.03% or 0.1% ointment and 1.0% pimecrolimus cream	100
2B	Tacrolimus is indicated in moderate-to-severe AD (flares and maintenance treatment based on SmPC). Tacrolimus can be used for the prevention of flares and to prolong flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring four or more times per year)	100
2C	Pimecrolimus is indicated in mild or moderate AD and can be used intermittently in the long term for the prevention of progression to flares	83.33
2D	TCIs suppress synthesis of pro-inflammatory cytokines. In the cytoplasm of the target cells, pimecrolimus and tacrolimus bind to the intracellular protein macrophilin-12, also called FKBP. Tacrolimus shows a threefold greater affinity to FKBP compared with pimecrolimus	100
2E	TCIs immunosuppressive activity results from suppressing calcineurin activity. The drugs have an anti-inflammatory activity due to T-helper activity affecting synthesis and release of pro-inflammatory cytokines. Tacrolimus and pimecrolimus inhibit mast cell and neutrophil activation and release of inflammatory mediators. Tacrolimus affects basophil and eosinophil function as well as function and induction of apoptosis in Langerhans cells	100

Table 3 Consensus statements on the efficacy of topical calcineurin inhibitors in adult and paediatric atopic dermatitis (AD) patients

	Statement	Consensus reached (%)
3A	The efficacy of both tacrolimus ointment and pimecrolimus cream has been demonstrated vs. placebo in clinical trials, in both the short- and long-term settings. In addition, proactive tacrolimus ointment therapy has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving the quality of life in adult patients and children	100
3B	Well-grounded evidence shows that in adult and paediatric AD patients, tacrolimus ointment is more effective than pimecrolimus cream, with a faster onset of action	100
3C	Data from adult and paediatric studies in patients with mild, moderate and severe disease support the superior efficacy of tacrolimus ointment when compared with pimecrolimus cream in the treatment of AD	100

Table 4 Consensus statements on the pharmacokinetics of topical calcineurin inhibitors (TCIs)

	Statement	Consensus reached (%)
4A	TCI absorption through the skin into circulation is minimal due to the large molecular size of the drugs. Pimecrolimus is more lipophilic than tacrolimus, and this results in slow penetration of TCI from the corneal layer rich in lipids into the hydrated lower epidermal layer	83.33
4B	Pimecrolimus permeates through the skin less than tacrolimus. Nevertheless, data from adult and paediatric pharmacokinetic studies show that tacrolimus ointment is associated with minimal systemic absorption and has no evidence of systemic accumulation in adult and paediatric patients with moderate-to-severe atopic dermatitis and extensive disease	100

Table 5 Consensus statements on the incidence of adverse events with topical calcineurin inhibitors

	Statement	Consensus reached (%)
5A	Data from studies in adults and children with mild, moderate and severe disease show that the incidence of adverse events, including local application site reactions, was low and comparable in tacrolimus-treated and pimecrolimus-treated patients	100

Table 6 Consensus statements on the safety concerns with the use of topical calcineurin inhibitors (TCIs) in atopic dermatitis (AD)

	Statement	Consensus reached (%)
6A	Burning sensation is a very common undesirable effect with both TCIs, with frequencies ≥1/10. Usually, it is of mild-to-moderate severity and tends to resolve within 1 week of treatment initiation	100
6B	In AD adult patients, there were no significant differences in the incidence of adverse events, including application site burning, between tacrolimus and pimecrolimus. No safety concerns were observed	83.33
6C	In AD paediatric patients, there were no significant safety and tolerability differences between tacrolimus and pimecrolimus	83.33
6D	Lymphoma incidence in TCI-treated patients was no higher than in the general population, and no causal relationship has been demonstrated between TCI use and an increased risk of lymphoma	100
6E	Epidemiological and clinical data challenge the validity of the warning placed on TCIs, which is based on theoretical concerns about a potentially associated risk of lymphoma. The American Academy of Dermatology (AAD) believes that these warnings confuse and unnecessarily worry people. Studies prove that with proper use, TCIs are not dangerous	100
6F	There is no scientific evidence of an increased risk of malignancy due to a topical treatment with TCIs	100

Evidence-based comment

Background of AD

In this general overview, the participants agreed on basic definitions of the disease and management strategy. AD was defined as an inflammatory, itching, chronic or chronically relapsing skin disease, with a very high prevalence affecting adults and mainly children in most countries of the world. It often occurs in families with a history of other atopic diseases, including bronchial asthma and/or allergic rhinoconjunctivitis.[9,10]

After AD has been diagnosed, disease severity has to be determined using dedicated scales. The standard approach is the 'Scoring of Atopic Dermatitis' (SCORAD),[10] but another commonly used scale to assess disease severity is the Eczema Area and Severity Index (EASI).[11]

Management of exacerbated AD represents a major therapeutic challenge, requiring effective short-term control of acute symptoms whilst maintaining the overall management plan of long-term stabilization, flare prevention and avoidance of side-effects.[9] To this end, anti-inflammatory treatment based on topical corticosteroids and TCIs should be used for the management of exacerbations and the proactive therapy of selected cases.[9,10] TCIs should be used for the management of exacerbations and continued with twice-weekly proactive therapy twice weekly for

several months. Unlike topical corticosteroids, TCIs are not associated with skin atrophy over the long-term use.[12,13] In a comparative study on quiescent AD, 4-week treatment with a corticosteroid (betamethasone valerate) adversely affected the biophysical properties of the skin barrier and reduced the concentration of natural moisturizing factors; on the other hand, tacrolimus improved skin barrier and increased hydration to levels similar to those of healthy skin.[14] Therefore, TCIs are specifically indicated in the long-term treatment of AD for the whole body and are preferred in certain sensitive areas including the face, intertriginous sites and anogenital area.[9,10,15]

What about the mechanism of action and therapeutic indications in AD?

At present, two TCIs are available for the treatment of AD in clinical practice: tacrolimus ointment available in two strengths (0.03% and 0.1%) and pimecrolimus available as a 1.0% cream.[15] Tacrolimus is indicated in moderate-to-severe AD for short-term treatment and long-term intermittent treatment of flares as well as for proactive therapy for the prevention of flares.[16] When used as maintenance therapy, tacrolimus has been shown to prolong flare-free intervals in patients who experience a high incidence of disease exacerbations (i.e. occurring four or more times per year). Pimecrolimus is indicated in mild-to-moderate AD.[17] Although pimecrolimus is not licensed for proactive management, it may be used in the prevention of acute exacerbation of the disease and can be used intermittently with corticosteroids.[17]

The mechanism of action of TCIs is to suppress synthesis of pro-inflammatory cytokines. Pimecrolimus and tacrolimus bind to the intracellular protein macrophilin-12, also known as FKBP, in the cytoplasm of target cells.[15] It is noteworthy that affinity to FKBP is threefold greater for tacrolimus compared with pimecrolimus.[18] Moreover, TCIs exert an immunosuppressive action by suppressing the activity of calcineurin and inhibiting mast cell and neutrophil activation. Considering the target cells involved in the action of TCIs, pimecrolimus exerts an action on T lymphocytes and mast cells whilst tacrolimus also reduces function of basophils and eosinophils and induces apoptosis of Langerhans cells.[15] In this way, tacrolimus has a broad spectrum of activity on the immune system.

What about efficacy in adult and paediatric AD patients?

Tacrolimus ointment and pimecrolimus cream have demonstrated efficacy in clinical trials in both short- and long-term therapy of AD.[7,19–22] However, a detailed description of results from these trials is beyond the scope of the present paper. In addition, proactive treatment of AD with 0.1% tacrolimus ointment for up to 1 year was shown to be effective and safe with a significantly reduced number of flares ($P < 0.001$ compared with vehicle ointment) and improved quality of life in adult patients.[22]

Tacrolimus ointment was found to be more effective than pimecrolimus cream in adult and paediatric patients with AD in a Cochrane meta-analysis which included 20 studies, with 5885 participants.[6] These findings are consistent with AD of varying degrees of severity and in adult and paediatric patients.[23,24] In a head-to-head study, tacrolimus treatment induced significantly greater improvements in the EASI score by week 3 compared with pimecrolimus, with improvements sustained until study end (a reduction of 57% from baseline with tacrolimus vs. 39% with pimecrolimus, $P = 0.0002$).[25]

What about pharmacokinetics?

The large molecular size of TCIs minimizes their absorption through the skin into circulation. Importantly, pimecrolimus is highly lipophilic, which results in its slow penetration from the corneal layer rich in lipids into the hydrated lower epidermal layer.[15] TCIs are associated with minimal systemic absorption, with no evidence of systemic accumulation in adult and paediatric pharmacokinetic studies.[26]

What about the incidence of adverse events?

A similar low incidence of adverse events, including local application site reactions, has been demonstrated in adult and paediatric patients with mild to very severe AD treated with either tacrolimus or pimecrolimus.[24] Burning sensation is a common undesirable event with both TCIs. It is usually mild-to-moderate in severity and tends to resolve within 1 week after treatment initiation.[16,17] No differences were identified in the incidence of adverse events, including application site burning, in adult patients treated with either tacrolimus or pimecrolimus[25]; similar findings have been reported in paediatric patients.[7,27] In addition, studies have shown that there is no increased risk in cutaneous infections (including herpes) in patients treated with tacrolimus.[6]

What about safety concerns?

An increased background incidence of lymphoma has been regarded as a safety concern in patients treated with TCIs.[28] However, it has been demonstrated that the incidence of lymphoma in TCI-treated patients is no higher than in the general population, and no causal relationship has been demonstrated between TCI use and an increased risk of lymphoma.[29] Moreover, epidemiological and clinical data challenge the validity of the warning issued by the United States Food and Drug Administration on TCIs, which is based on theoretical concerns about a potentially associated risk of lymphoma.[29,30] To this end, the American Academy of Dermatology believes that 'these Warnings confuse and unnecessarily worry people. Studies prove that with proper use, topical pimecrolimus and tacrolimus are not dangerous'.[29]

Clinical experience on hot topics not addressed in major literature

The participants also discussed current hot topics concerning the use of TCIs for the treatment of AD which, by their nature, cannot be formally addressed in clinical trials or large observational studies. The key outcomes of this discussion are provided below.

Cream vs. ointment

Delivery vehicles play a major role in contributing to the efficacy and safety of topical treatments in the dermatological setting.[31,32] Of the two TCIs available for the treatment of AD, tacrolimus ointment and pimecrolimus cream, the lipophilic properties of an ointment permit better penetration and enhance moisturizing activity due to its higher concentration of oil compared with a cream-based treatment. Indeed, AD can be considered a dry skin condition, and the use of tacrolimus ointment may aid healing by keeping the skin moist for longer. Therefore, in some skin conditions, such as AD, it may be preferable to initiate treatment with an ointment given its moisturizing activity that can help deliver a rapid response. However, for some specific sites (e.g. face, and especially during summer), patients may prefer an agent characterized by a lower activity but with a more comfortable application, such as a cream. Clinicians should be aware of these potential differences and tailor therapy accordingly, with the aim to ensure proper compliance.

Tacrolimus multiple strength vs. pimecrolimus single dosage

The availability of two dosages of tacrolimus may offer more flexibility in clinical practice compared with the single dosage available for pimecrolimus. Indeed, the 0.03% tacrolimus formulation shows high efficacy in the treatment of children with mild-to-moderate AD.[33] However, the more potent 0.1% formulation of tacrolimus may also be needed in children, especially in particular cases such as the treatment of lichenified lesions on the extremities. Treatment with tacrolimus 0.1% is recommended in adult patients, and the 0.03% formulation is effective in mild-to-moderate AD and in AD located on the eyelid.[33] The double formulation allows such flexibility in the choice of the treatment, for the specific indication required.

TCIs contact allergy

Contact allergy has been anecdotally reported in association with TCI treatment.[34–37] It appears that most cases of contact allergy were related to pimecrolimus use, possibly due to the presence of cetyl alcohol, stearyl alcohol or polypropylene glycol, which are known to cause contact dermatitis.[36,38] However, the participants agreed in not considering contact allergy as differentiating issues between the two TCIs, because of the poor evidence available in the literature and the well-established safety profile of both compounds in clinical practice. Therefore, contact allergy should not be considered a safety concern for TCI therapy in AD patients.

Table 7 Factors differentiating tacrolimus from pimecrolimus, according to participants' opinion and current evidence

More favourable pharmacokinetic (e.g. higher penetration in the skin) and pharmacodynamic (e.g. higher affinity for FKBP) properties of tacrolimus compared with pimecrolimus
Superior efficacy of tacrolimus as compared with pimecrolimus according to current clinical evidence
Fast and sustained action of tacrolimus
The ointment formulation of tacrolimus could be an advantage over cream formulation
Potential role of tacrolimus within combination regimens with corticosteroids

Burning sensation management

Some patients, almost all cases in adults, experience a burning sensation during TCI therapy.[39,40] This sensation, which is likely related to mast cell activity, has an intensity associated with disease severity and long-term previous therapy with corticosteroids.[41]

It is noteworthy that the burning sensation tends to resolve within 1 week of treatment initiation, and therefore, patients should be educated to not interrupt therapy with TCIs if this event occurs; by continuing therapy, the skin barrier improves and the intensity of the burning sensation decreases.[40,42] If necessary, the administration of non-steroidal anti-inflammatory drug (e.g. ibuprofen) or paracetamol can be recommended during the first days of treatment with tacrolimus to reduce the burning sensation. Moreover, the use of acetylsalicylic acid was shown to be very efficient in one study.[43]

Superinfection

Patients with active eczema often present *Staphylococcus aureus* superinfection, which may require antibiotic therapy; however, when the lesions heal, the infection regresses due to the restored skin barrier.

Figure 2 Outcome of a 1-week treatment with tacrolimus ointment in a paediatric patient with atopic dermatitis.

Figure 3 Short (3 months) and long (8 years) outcomes of treatment with tacrolimus ointment in a patient with erythrodermic atopic dermatitis.

Figure 4 Outcome of a treatment regimen based on topical corticosteroids, tacrolimus and emollients.

Vaccination concern

The participants agreed that there is no relationship between TCI application and vaccination efficacy, in line with previous reports.[44,45]

Expert opinion: differentiation between TCIs in clinical practice

According to available evidence and the participants' opinion, TCIs can represent a suitable therapy for AD. Selection of the specific TCI should be based on a number of factors which differentiate tacrolimus from pimecrolimus (Table 7).

Firstly, the choice of tacrolimus treatment is driven by its superior efficacy compared with pimecrolimus, likely due to its more favourable pharmacodynamic properties such as greater affinity for FKBP. This high efficacy has a prompt onset of action and is sustained over the long term, with proactive treatment contributing to normalize the skin condition without any relevant safety concerns or damage to the skin (Figs 2 and 3). Tacrolimus is effective in sensitive and non-sensitive areas, with the only possible exception being hand eczema, a condition in which tacrolimus is often not effective enough.

Notably, long-term results with tacrolimus are better if treatment is used as monotherapy, as this leads to a normalization of the skin barrier. If corticosteroids are used together with tacrolimus, they may reduce inflammation but weaken the skin barrier at the same time. The only exception is hand eczema, where tacrolimus is often not effective enough, probably due to the thickness of the skin (Fig. 4).

Importantly, an ointment formulation could be an advantage in several cases, according to disease severity and the involvement of specific body areas. In particular, ointments may grant a more evident moisturizing effect and therefore may be suitable for the treatment of AD. Collectively, these properties of tacrolimus may result in a greater efficacy and be associated with a cost-saving for the healthcare system, as compared with pimecrolimus.[46] Consequently, tacrolimus may be considered favourably for the treatment of AD in both adult and paediatric patients.

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Appendix: Search criteria

('Dermatitis, Atopic'[Majr] OR 'atopic dermatitis'[tiab] OR 'atopic eczema'[tiab] OR 'atopic eczemas'[tiab] OR 'infantile eczema'[tiab] OR 'atopic neurodermatitis'[tiab] OR 'disseminated neurodermatitis'[tiab] OR (atopic[tiab] AND (dermatitis [tiab] OR eczema*[tiab] OR dermatitides[tiab]))) AND ('Calcineurin Inhibitors'[Majr] OR 'Tacrolimus'[Majr] OR 'pimecrolimus' [Supplementary Concept] OR 'topical calcineurin inhibitors'[tiab] OR 'topical calcineurin inhibitor'[tiab] OR TCIs[tiab] OR TCI[tiab] OR tacrolimus[tiab] OR pimecrolimus[tiab] OR 'calcineurin inhibitors'[tiab] OR 'calcineurin inhibitor'[tiab] OR 'calcineurin antagonist'[tiab] OR 'calcineurin antagonists'[tiab] OR (calcineurin*[tiab] AND (antagonist*[tiab] OR inhibitor*[tiab])))) AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR Guideline[ptyp] OR Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR systematic[sb] OR Review [ptyp]))) OR (('Dermatitis, Atopic'[Majr] OR 'atopic dermatitis'[tiab] OR 'atopic eczema'[tiab] OR 'atopic eczemas'[tiab] OR 'infantile eczema'[tiab] OR 'atopic neurodermatitis'[tiab] OR 'disseminated neurodermatitis'[tiab] OR (atopic[tiab] AND (dermatitis[tiab] OR eczema*[tiab] OR dermatitides[tiab]))) AND ('Calcineurin Inhibitors'[Majr] OR 'Tacrolimus'[Majr] OR 'pimecrolimus' [Supplementary Concept] OR 'topical calcineurin inhibitors'[tiab] OR 'topical calcineurin inhibitor'[tiab] OR TCIs[tiab] OR TCI[tiab] OR tacrolimus[tiab] OR pimecrolimus[tiab] OR 'calcineurin inhibitors'[tiab] OR 'calcineurin inhibitor'[tiab] OR 'calcineurin antagonist'[tiab] OR 'calcineurin antagonists'[tiab] OR (calcineurin*[tiab] AND (antagonist*[tiab] OR inhibitor*[tiab])))) AND (inprocess[sb] OR publisher[sb]))

